UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,606	01/05/2004	Mark J. Ratain	ARCD:389US	2944

32425 7590 07/26/2006

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
BAUSCH, SARAE L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,606	RATAIN ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *6-14,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06/07/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/05 05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 1-25 in the reply filed on 05/03/2006 is acknowledged. In a supplemental response mailed 05/18/2006, Applicant's elected, without traverse, the polymorphism –3279 and this election is acknowledged. As such claims 1-5, 15-23 are being examined on the merits. It is noted that claims 22-23 will be examined to the extent the claims read on the elected invention of –3279 polymorphism.

2. Claims 6-14 and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 05/03/2006 and the supplement response filed on 05/18/2006.

Drawings

3. The drawings filed on 06/07/2004 are acceptable.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. There are no sequence identifiers for the sequences listed throughout the specification. Applicant is required to thoroughly review the specification and comply with all sequence rules. For example, the following sequence in the specification do not have sequence identifiers: figure 1.

For any response to this office action to fully responsive, applicants are required to comply with sequence rules.

Claim Rejections - 35 USC § 112- Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5 and 15-23 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are broadly drawn to a method for risk of irinotecan toxicity as well as optimizing the dose of irinotecan by determining the presence of "any" polymorphism in one or

both UGT1A1 genes which is in linkage disequilibrium with "any" UGT1A1 TA repeat in "any" patient. The claims are further drawn to administering to the patient irinotecan and a second agent to reduce excretion of an active irinotecan species through the bile. The claims are further drawn to evaluating the risk of irinotecan toxicity by determining the nucleotide sequence at position –3279G>T of a patient and indicating a low level of UGT1A1 activity.

Guidance in the Specification

The specification asserts a method for determining the presence or absence of polymorphisms within a uridine diphosphate glucuronsyltransferase I AI (UGT1A1) promoter and correlating these polymorphisms with toxic effects of irinotecan as well as evaluating the risk of an individual for developing irinotecan toxicity (see page 2, lines 12-18). The specification asserts a method for determining if a treatment has a propensity to adversely affect a patient or what treatment may be appropriate or inappropriate for a particular patient by correlation with UGT1A1 genetic variation (see page 5, lines 7-12). The specification asserts that significant linkage disequilibrium between a (TA) polymorphism and variants in the phenobarbital-responsive enhancer module (PBREM) or other variants within or outside the UGT1A1 gene locus indicates that patients possessing such other variants may be at risk of irinotecan toxicity (see page 5, lines 25-29).

The specification teaches that irinotecan treatment is associated with significant toxicity and the main severe toxicities of irinotecan are delayed diarrhea and myelosuppression. The specification teaches that grade 3-4 diarrhea occurred in one third of patients and was dose limiting and teaches that a three-weekly regimen is significantly lower than a weekly regimen for grade 3-4 diarrhea. The specification teaches that grade 3-4 neutropenia is experienced in 30-

40% of patients experiencing both weekly and three weekly regimens (see page 4, lines 5-20). However, the specification does not teach a method of evaluating the risk of "any" irinotecan toxicity in "any" patient by detecting "any" polymorphism in linkage disequilibrium with any TA repeat in the UGT1A1 gene.

The specification teaches that metabolism of SN-38, an active metabolite of irinotecan, via glucuronidation represents a mechanism to protect patients from the toxic effects of irinotecan and thus a reduction of SN-38 glucuronidation contributes to the probability that toxicity associated with irinotecan may be experienced in patients (see page 4, last paragraph cont'd to page 5, first paragraph), however the specification does not teach a correlation between the metabolism of SN-38 with any polymorphism in linkage disequilibrium with any TA repeat in the UGT1A1 gene.

The specification asserts that patients possessing significant linkage disequilibrium between a (TA) polymorphism and variants in the PBREM or within or outside the UGT1A1 gene locus indicates that patient may be at risk of irinotecan toxicity (see page 5, lines 25-28) and the relationship between PBREM-(TA)n haplotype and glucuronidation rate of the UGT1A1 substrate of SN-38 may be used to correlate the genotype

The specification teaches that analysis of UGT1A1 genetic variation in relation to severe toxicity after different irinotecan-based regimens has been conducted in Japanese patients but a prospective evaluation in a large trial has not been preformed and the problem of identifying the effects of various promoter polymorphism combinations on expression of UGT1A1 for determination of UGT activity levels remains and improved methods for evaluating of risk of irinotecan toxicity in an individual or patient are still needed.

The specification asserts that the evaluation of the promoter polymorphism may be used to optimize the dose of irinotecan or other compounds for treatment of a patient or to reduce their toxicity (see page 7, lines 24-26), however the specification does not teach what results of evaluating the promoter polymorphism would allow for setting a dose of the compound. For example, if a TA repeat of 5 was determined in any individual, the skilled artisan based on the teaching in the specification would not know what dosage of the compound should be administered. The specification does not provide any guidance for correlating the results of the method of the evaluating the risk of irinotecan toxicity with setting a dose of irinotecan.

While the specification demonstrates a study of genotyping 63 patients who were administered irinotecan and had 9.5% frequency of grade 4 neutropenia irinotecan toxicity (see page 59-60 and figure 4) which was found to be more common with genotype 7/7 compared to 6/7 and 6/6 (see page 60, lines 1-5); the specification does not teach a method of evaluating the risk of "any" irinotecan toxicity by analyzing the presence of any polymorphism in linkage disequilibrium with any UGT1A1 TA repeat. The specification provides no data for the association of any polymorphism, including –3279 polymorphism of UGT1A1 and the correlation of any irinotecan toxicity. The specification asserts that the relationship between UGT1A1 genotype and severity of diarrhea could not be determined due to the low frequency of sever diarrhea in patients (see page 60, lines 18-24). The specification provides inconclusive data of the (TA) polymorphism with –3279 polymorphism and the correlation of any irinotecan toxicity in any patient. For example, the teaching in the specification show that three patients had grade 3 diarrhea were one patient was 7/7 genotype while the other two patients were 6/7 and 50% of patients with a 7/7 genotype had grade 4 neotrepenia upon administration of

irinotecan. The specification does not indicate how to determine which 50% of individuals with a (TA)7 in linkage disequilibrium with any polymorphism in the UGT1A1 gene will have a risk of irinotecan toxicity. Furthermore the specification provides no information on how to determine the dosage of irinotecan to be administered to a patient based on any polymorphism in linkage disequilibrium with the (TA) repeat. Additionally, the specification provides no correlation between the presence of –3279 polymorphism and (TA) repeats in the UGT1A1 gene and irinotecan toxicity.

It is unclear from the lack of guidance in the specification how to estimate the risk of irinotecan toxicity by determining the presence of any polymorphism of UGT1A1 polymorphism in linkage disequilibrium with any TA repeats located in the UGT1A1 gene. The specification only gives limited guidance with respect to toxicity upon administration of irinotecan and correlation with genotyping of the UGT1A1 genomic DNA and association of the TA repeats in the TATA box of the UGT1A1 promoter region. The data in the specification demonstrates that the following genotypes were associated with neutropenia grade 4: 50% of patients have the 7/7 TA genotype of UGT1A1, 12.5% of patients have the 6/7 TA repeats, and 0% of patients had 6/6 TA repeats (see page 60, lines 1-4). The specification does not demonstrate any toxicity with any polymorphism, including –3279 polymorphism of UGT1A1gene in linkage disequilibrium with any TA repeat of UGT1A1 gene. The specification does not teach which TA repeats is correlative to leucopenia or diarrhea, much less "any" other toxicity of administration of irinotecan. If the skilled artisan assayed an individual and found the individual to have a 7/7 repeat of UGT1A1 promoter region in linkage disequilibrium with –3279 polymorphism, how would the skilled artisan know if the individual would have the risk of developing toxicity to

irinotecan? How would the skilled artisan know much of irinotecan to administer to the patient? The specification does not teach a predictive correlation with variants of UGT1A1 and administration of irinotecan. Furthermore, the specification does not teach any association of position -3279 alone or with a variant of TA repeats of UGT1A1 with "any" toxicity.

The specification does not provide any guidance with which genotype is predictably correlative to leucopenia, neotropenia, or diarrhea, much less "any" toxicity of irinotecan, for example did the volunteers have any other side effects conditions (nausea, headache, malaise, loss of appetite, etc) that would affect estimating the risk of toxicity and possibly affect the correlation with genotype of UGT1A1? Based on the teachings in the specification, it is unclear how the analysis of TA repeats in UGT1A1 gene and position -3279 correlates to evaluating the risk of "any" irinotecan toxicity or how to determine the dosage of compound to administer based upon the variant present.

The specification envisions hypothetical situations where the presence of a variant of UGT1A1 gene in linkage disequilibrium with any TA repeats could be used to determine "any" toxicity of administration of irinotecan, and the results further be used to determine the dosage of irinotecan. The specification appears to be conceiving of possible scenarios where the genotype of the UGT1A1 gene of an individual could be used to determine a risk of toxicity and that these results could indicate amount of dosage of irinotecan, however, it is unclear how one of skill in the art would correlate the presence of a specific genotype with toxicity of irinotecan or how one of skill in the art would determine the dosage of irinotecan based on the genotype present in an individual and the limited guidance in the specification and the prior art.

Working Examples

The specification demonstrates a study of genotyping 83 human livers which comprised 68% Caucasians, 18% African-Americans, 1% Asians and 2% others (see example 1, page 44-48) and genotyping and determining the linkage disequilibrium of 103 samples for (TA) polymorphism and the PBREM region of UGT1A1 (see example 2-4, pages 49-52). The specification demonstrates a working example of genotyping 63 patients that were administered irinotecan (see example 7, pages 59-62) by analysis of TA repeats in the TATA box of UGT1A1 and presence of –3279T and –3156A of UGT1A1 gene (see page 59, lines 20-27). The specification demonstrates the toxicity of diarrhea and neutropenia was analyzed and demonstrate that 9.5% of patients had grade 4 neutropenia (page 59, line 30), 5% patients had grade 3 diarrhea and no patients had grade 4 diarrhea (see page 60, lines 18-24). The specification teaches that the low frequency of severe diarrhea did not allow any formal statistical analysis and teach that 50% of patients had genotype 7/7, 12.5% had 6/7 and 0% had 6/6 genotype with grade 4 neutropenia (see page 60, lines 1-4). The specification teaches analysis of –3156G>A variant with TA7 individuals and neutropenia (see page 60, lines 5-17), however the specification does not teach any analysis of –3279T with any toxicity.

The specification does not teach which genotype of UGT1A1 predictably correlates to an setting of a dosage such that the skilled artisan would be able to predictably correlate the results of genotyping study to determine if irinotecan would give any toxicity or determine the dosage of the compound to be administered.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

The unpredictability of the art and the state of the prior art

The prior art teaches that there are many parameters that need to be evaluated prior to using polymorphism and gene expression as a test to determine if "any" toxicity of irinotecan administered to a patient will occur. Furthermore, the prior art teaches that the parameters that need to be addressed in order to conduct a study on correlating polymorphisms in gene expression yield gaps in information that are needed to complete a thorough screening of gene expression effects.

Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly

common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Applicant's own post filing art, (Innocenti et al, J. Clin. Onc. 2004 22(8):1382-1388), teach that a study of 66 patients was not a precise assessment of the sensitivity of the TA indel diagnostic test (see page 1386, 2nd column, 2nd full paragraph) and teach that a precise assessment of the sensitivity of TA indel diagnostic test would require a larger number of patients, as also indicated by the quite wide 95% CI of the test parameters (results are similar to data presented in the instant specification) (see page 1386, 2nd column, 2nd full paragraph). Innocenti et al. teach that –3279G>T variant was not associated with bilirubin when TG6/TG6 were compared to TG6/GC6 and when TG6/GA7 patients were compared with GG6/GA7 patients (see page 1385, 2nd column, 1st paragraph). Additionally, applicant's own post filing art, (Innocenti et al. Pharmacogenetics and Genomics 2005, 15:295-301) describe common haplotypes in the UGT1A1 gene and highlight the important ethnic differences in the composition between Asians and Caucasians (see page 300, 1st column, 1st full paragraph). Innocenti et al. teach that future studies are planned to evaluate the linkage disequilibrium in large collection of samples of African origin and if the functional effect of UGT1A1 haplotype will be confirmed in further preclinical studies the phenotypic consequence of these haplotypes on the pharmacokinetics and pharmacodynamis of substrates of UGT1A1 should be evaluated

(see page 300, 1st column last sent. Con't to 2nd column). Applicants own post filing art teach that the haplotype of the UGT1A1, including –3279G>T and TA repeats, is different among Caucasian and Asians and further studies are needed to evaluate the haplotypes present in other races, as well as for correlation of haplotypes and drug interactions.

Furthermore, Applicants own art, (Innocenti et al., Pharmcogenetics, 2002, 12:725-733) teach linkage disequilibrium in Caucasians was highly significant between –3278 and the (TA) polymorphism (see abstract). Innocenti et al. teach that the haplotype is different between Caucasians and African-Americas (see abstract). Innocenti et al. teach that no statistical difference was observed when SN-38 glucuronidation rates were compared between –3279 haplotypes and the functional significance of the –3279G>T requires further testing (see page 731, 2nd column, 1st paragraph). Innocenti et al. teach that haplotypic structure of the UGT1A1 promoter is likely to vary in different ethnicities (see page 732, 1st column, 1st full paragraph). Innocenti et al. teach that finding a haplotype-pheotype correlation is hampered by the limited sample size of haplotype pairs for each (TA) genotype, as well as environmental variables that affect UGT1A1 expression, such as smoking habit, alcohol intake, previous medications and such factors might have a negative impact on association studies with limited sample size (see page 732, 2nd column, 1st full paragraph). The sample size presented in Innocenti et al. (2002) is the same sample size disclosed in the instant specification and as such, the limited sample size coupled with environmental variables, as taught by Innocenti et al. is unpredictable in correlating the haplotype of any patient with irinotecan toxicity (phenotype).

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate genotyping of any patient based on presence of the number of TA

repeats in the promoter region and any polymorphism of the UGT1A1 gene, including –3279G>T to evaluate the risk of any irinotecan toxicity or determine the dosage to be administered of irinotecan.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to correlation of any polymorphism of the UGT1A1 gene in linkage disequilibrium with any TA repeat to "any" toxicity of irinotecan and the lack of guidance with regard to correlating the variant of UGT1A1 gene to the dosage of irinotecan the quantity of experimentation in this area is extremely large. The skilled artisan would have to determine a predictable correlation between variants of UGT1A1 gene that are in linkage disequilibrium that would result in "any" adverse side effect (toxicity) by the administration of irinotecan before attempting to determine the amount of dosage of the compound. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine which genotype is present upon administration of irinotecan in all patients (human, dog, cat, etc.) and which genotype is associated with "any" side effect – which encompasses more than neotrepenia, diarrhea and leucopenia, for example it could include headaches, mild nausea, or the efficacy of the drug. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if the polymorphism is in linkage disequilibrium with the TA repeats and this is in fact detecting adverse side effect due to administration of irinotecan and is associated with the dosage of the compound. There is still a significant amount of unpredictably in identifying genes and within the human gene, a skilled artisan would have to perform a large exhaustive assay to test for genotypes in a large study pool, including a multi-ethnic study, as taught by Innocenti et al. to

determine if the genotypes identify adverse side effects due to administration of a compound and then determine how to determine the dosage based on the genotype present. This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the lack of guidance on how to predictably correlate variants of the UGT1A1 gene to estimating the risk of "any" toxicity by administration of irinotecan and then further determining the dosage of irinotecan, the large quantity of research required to define the lack of guidance provided in the specification, the absence of working examples, and the negative teaching in the prior art balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make the claimed invention.

Claim Rejections - 35 USC § 112-Description

7. Claims 1-5, 15-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a method for evaluating the risk of irinotecan toxicity in a patient by determining the presence of "a" polymorphism in one or both of UGT1A1 gene wherein the polymorphism is in linkage disequilibrium with "a" UGT1A1 TA repeat. Claim 2 limits the polymorphism to "all or part of the 5' flanking region" of the UGT1A1 gene. Claim 5 limits the polymorphism to –3279 G>T however the claim encompass any "TA" repeat present in any

region of the UGT1A1 gene. While the specification teaches the TA repeats are in the TATA box of UGT1A1 (see page 3, lines 1-7) and teach significant linkage disequilibrium between a (TA) polymorphism and variants in the PBREM or other variants within or outside the UGT1 gene locus indicates that patients possessing such other variants may be at risk of irinotecan toxicity (see page 5, lines 25-28), neither the specification nor the art teach "any" polymorphism in linkage disequilibrium with "any" TA repeat in the UGT1A1 gene. Furthermore, the specification does not describe any TA repeat in linkage disequilibrium with any polymorphism in the UGT1A1 gene that is associated with the risk of irinotecan toxicity. The specification asserts that the TA repeats maybe be 5, 6, 7, 8, or more TA repeats and the polymorphisms are at position –3440, -3401, -3279, -3177, -3175, and -3156 (see page 6, lines 20-30), however the specification does not teach "any" polymorphism of the UGT1A1 in linkage disequilibrium with "any" TA repeats in the UGT1A1 gene. The specification correlates grade 4 neotrepenia with –3156 polymorphism and a 6/6 TA repeat but does not correlate any other polymorphism in linkage disequilibrium with any other TA repeats with any irinotecan toxicity. Functional genotyping studies that could distinguish the presence of polymorphisms in linkage disequilibrium with the TA repeats of UGT1A1 gene necessary to predictably correlate the risk of irinotecan are missing from the specification.

The recitation of "all or part of the 5' flanking region of one or both UGT1A1 genes" in claim 2 encompasses many variants of the UGT1A1 gene and the specification does not disclose or provide working examples illustrating which parts of the 5' flanking region would be functionally active to determine the risk of irinotecan toxicity. Thus the scope of the claims include numerous functional variations of UGT1A1 gene and the genus is highly variable

because a significant number of differences between genus members is permitted. The specification and claim does not provide any guidance as to which region of the UGT1A1 is required to identify the polymorphisms in the UGT1A1 to determine the risk of irinotecan toxicity. The specification does not describe any functional assay that would allow one of skill in the art to determine if any region with as few as two nucleotides in length from any source would be predictably correlative of determine the polymorphism in the UGT1A1 gene.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Claim Rejections - 35 USC § 112- Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-5 and 15-23 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a). Claim 1-5 and 15-23 recites a method for evaluating the risk of irinotecan toxicity in a patient however the final process step is determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat. Accordingly, the claim is ambiguous because the preamble recites a limitation that is not recited in any of the process steps, there is not a clear nexus between the preamble and the process step, and it is not clear if the process steps will accomplish the claimed method. Applicant should amend the claims to indicate how the step of determining the presence of a polymorphism in one or both UGT1A1 genes of the patient results in evaluating the risk of irinotecan toxicity.

(b). Claim 2 is rejected as vague and indefinite for using the terminology "all or part of 5' flanking region". It is not clear what "all or part of the 5' flanking region" features are, nor what else the claimed nucleic acid sample might comprise. The phrase "all or part of 5' flanking region" in claim 2 is a relative term that renders the claim indefinite. The phrase "all or part of 5' flanking region" is not defined by the claim, the specification does not provide a standard fro ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(c). Claim 3 is vague and indefinite. Claim 3 recites "analyzing a glucuronidation rate associated with the polymorphism" however it is unclear how this further limits the claimed method of evaluating the risk of irinotecan toxicity. Claim 1 does not recite a glucuronidation rate and it is unclear how determining a glucuronidation rate will result in determining the risk of irinotecan toxicity.

(d). Claim 21 recites the limitation of "a second agent" however this recitation renders the claim indefinite. It is unclear how administration of a second agent to the patient further limits the claimed invention of evaluating the risk of irinotecan toxicity. Furthermore, claim 21 depends from claim 20 and claim 1 and neither claims recite a first agent. There is insufficient antecedent basis for this limitation in the claim.

(e). Claim 23 recites the limitation "the UGT1A1 activity" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 23 depends from claim 22 and claim 22 does not recite a UGT1A1 activity. Furthermore claim 23 recites "whereby identification of a guanine residue indicates the patient does not have a low level of activity". This recitation renders the claim vague and indefinite as there is no nexus between indicating the patient does not have a low level of UGT1A1 activity and risk of irinotecan toxicity. It unclear how not having a low level of activity results in the risk of irinotecan toxicity.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-5 and 15, 17-19, 22-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Innocenti et al. (Pharmacogenetics 2002 12:725-733).

With regard to claim 1, Innocenti et al. teach genotyping the UGT1A1 gene and determining linkage disequilibrium and haplotype structure of the UGT1A1 promoter (see page 729, 1st column, 1st full paragraph). Innocenti et al. teach determining the TA repeats of the UGT1A1 gene and polymorphisms in the UGT1A1 gene (see table 3, page 729).

With regard to claim 2, Innocenti et al. teach amplifying DNA by PCR by PCR primers that flank the polymorphic TA locus in the promoter region of the UGT1A1 gene (see genotyping (TA) polymorphism, page 726).

With regard to claim 3-5, Innocenti et al. teach determining the –3279G>T polymorphism and TA repeats of 6 TA repeats (see table 3, page 729).

With regard to claim 15, Innocenti et al. teach UGT1A1 activity was measured as SN-38 glucuronidation rates in 83 human livers and determined the association with the number of TA repeats and haplotypes (see page 729, 2nd column, 2nd and last paragraph and figure 2).

With regard to claim 17-19, Innocenti et al. teach genotyping of TA repeat polymorphism by PCR amplification (hybridization assay) by PCR primers that distinguish the size of the amplicons to determine the number of TA repeats (allele-specific amplification assay) (see

genotyping TA polymorphism, page 726). Innocenti et al. teach sequencing the PBREM promoter region of the UGT1A1 gene (see sequencing of PBREM, page 726).

With regard to claim 22-23, Innocenti et al. teach determining the nucleotide sequence at position –3279G>T in UGT1A1 (see table 3, page 729) and teach that the SN-38 glucuronidation (UGT1A1 activity) was reduced for variants –3279G>T (see page 731, 1st column, 1st paragraph).

It is noted that claim 1 and 22 recites a method for evaluating the risk of irinotecan toxicity in a patient. The preamble does not correlate with the active method steps of the claim and the final process step does not relate back to the preamble. The active method step is one of determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat and neither claim 1 or 22 recites how analyzing determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat relates to estimating the risk of irinotecan toxicity in a patient nor do the claims recite how a compound, such as irinotecan relates polymorphism in UGT1A1 in linkage disequilibrium with the TA repeats of UGT1A1. Therefore, Innocenti et al. anticipate the claimed method, which requires the active step of determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat.

12. Claims 1-2, 4 and 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Hasegawa et al. (US 2004/0058363, filing date 12/12/2000).

With regard to claim 1-2, and 4, Hasegawa et al. teach genotyping the TATA box of

UGT1A1 gene promoter region and codon 71 and 229 of the UGT1A1 gene (see paragraph 98-103). Hasegawa et al. teach an association of the number of TA repeats (5-8, claim 4) and polymorphism in codon 71 and 229 and irinotecan toxicity (see paragraph 123-125, 131).

With regard to claim 15, Hasegawa et al. further teach analyzing the bilirubin levels of the patients (glucuronidation rate) (see paragraph 121).

With regard to claim 16, Hasegawa et al. teach lowering the actual amount of irinotecan in patients (optimizing a dose of irinotecan) (see paragraph 121 and 134).

With regard to claim 17-19, Hasegawa et al. teach PCR amplification of the variant sequence of the promoter region of the UGT1A1 gene and determining the number of TA repeats (hybridization assay, allele specific amplification assay). Hasegawa et al. teach sequencing the PCR product (claim 18) (see paragraph 123-125 and paragraph 59-60).

With regard to claim 20-21, Hasegawa et al. teach administration of irinotecan to patients and loperaminde to patients suffering from severe toxicity (second agent) (see paragraph 96).

13. Claims 1-2, 4 and 15-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ando et al. (Cancer Research 2000 60:6921-6926).

With regard to claim 1-2 and 4, Ando et al. teach genotyping the TATA box of UGT1A1 gene promoter region and codon 71 and 229 of the UGT1A1 gene (see table 5, page 6924). Ando et al. teach an association of the number of TA repeats (5-8, claim 4) and polymorphism in codon 71 and 229 and irinotecan toxicity (see page 6923, 2nd column, 2nd full paragraph).

With regard to claim 15, Ando et al. further teach analyzing the bilirubin levels of the patients (glucuronidation rate) (see page 6923, 2nd column, last paragraph).

With regard to claim 16, Ando et al. teach lowering the actual amount of irinotecan in patients (optimizing a dose of irinotecan) (see page 6923, 1st column, 1st paragraph).

With regard to claim 17-19, Ando et al. teach PCR amplification of the variant sequence of the promoter region of the UGT1A1 gene and determining the number of TA repeats (hybridization assay, allele specific amplification assay). Ando et al. teach sequencing the PCR product (claim 18) (see page 6922, genotyping).

With regard to claim 20-21, Ando et al. teach administration of irinotecan to patients and loperaminde to patients suffering from severe toxicity (second agent) (see table 3, page 6923, 2nd column, 1st full paragraph).

It is noted that claim 1 recites a method for evaluating the risk of irinotecan toxicity in a patient. The preamble does not correlate with the active method steps of the claim and the final process step does not relate back to the preamble. The active method step is one of determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat and claim 1 recites how analyzing determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat relates to estimating the risk of irinotecan toxicity in a patient nor do the claims recite how a compound, such as irinotecan relates polymorphism in UGT1A1 in linkage disequilibrium with the TA repeats of UGT1A1. Therefore, Ando et al. anticipate the claimed method, which requires the active step of determining the presence of a polymorphism in one or both UGT1A1 genes of the patient wherein the polymorphism is in linkage disequilibrium with a UGT1A1 TA repeat.

Conclusion

14. No claims allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Sarae Bausch, PhD.
Examiner
Art Unit 1634
07/18/2006

CARLA J. MYERS
PRIMARY EXAMINER